

Penicillin-Allergie

– aus Sicht der Allergologie

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Interessenskonflikt

Vorträge: AbbVie, ALK, Bayer, Biotest, Eli Lilly, Leti, Sanofi

Beraterung: Allergopharma

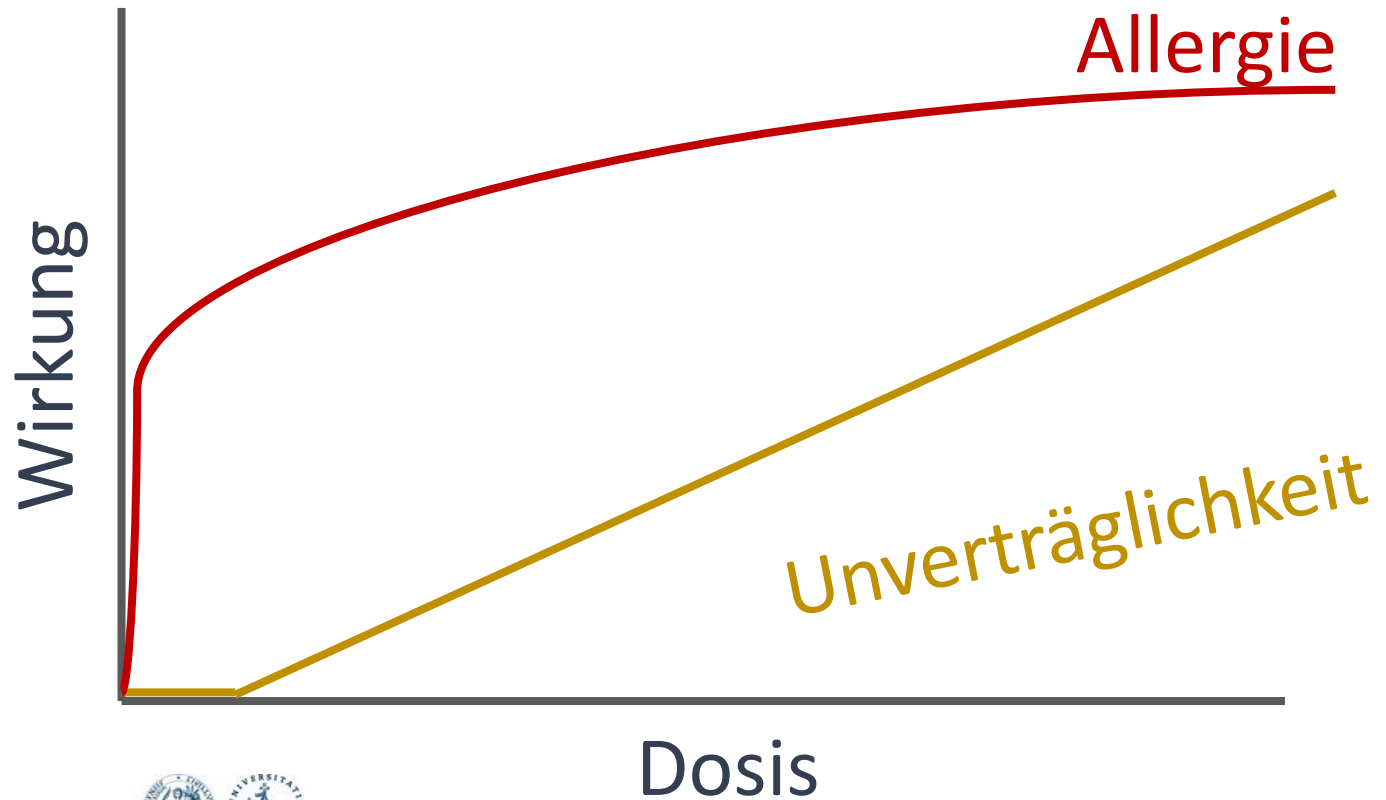
Themenverbundenheit: keine.

- Häufig berichtet – selten wirklich vorliegend
- Was ist eine allergische Reaktion?
- unterschiedliche Mechanismen – spezifisches Reaktionsmuster
- S2k-Leitlinie: „Diagnostik bei Verdacht auf eine Betalaktamantibiotika“

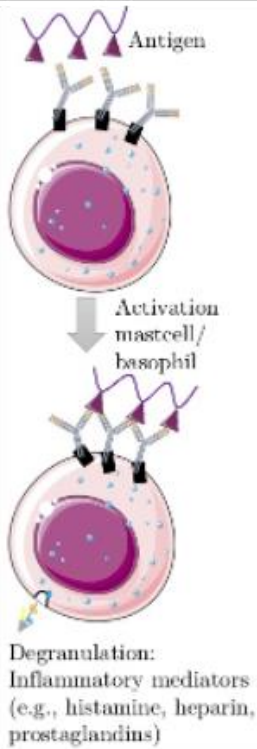
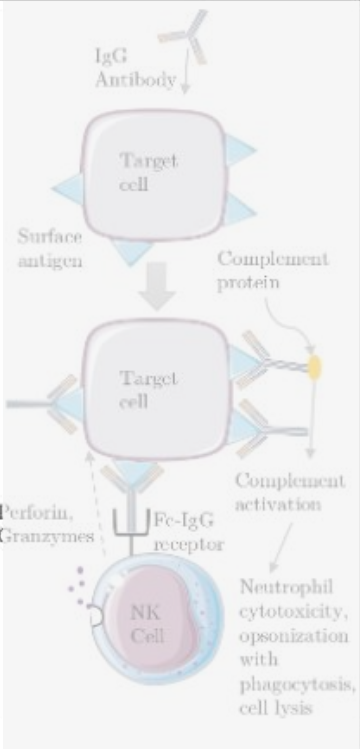
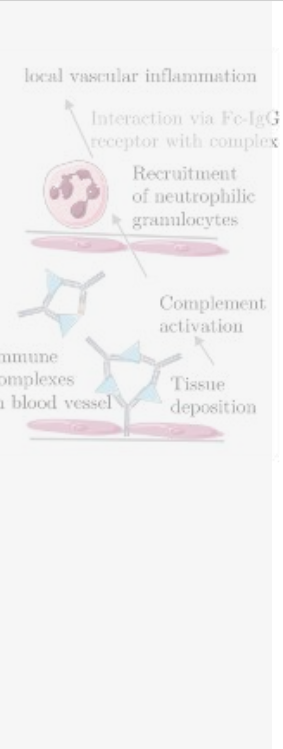
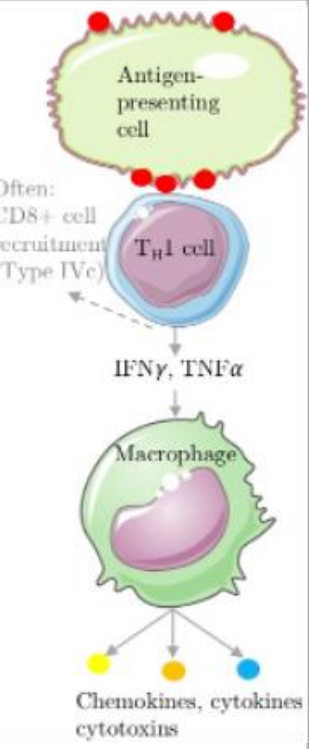
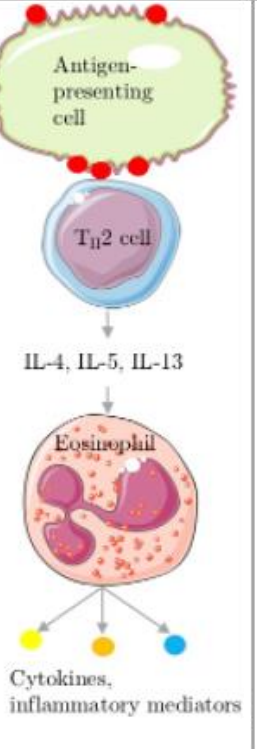
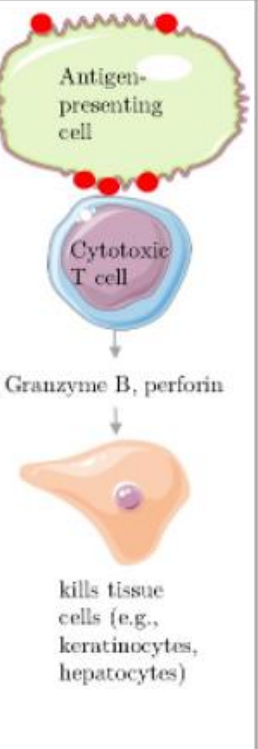
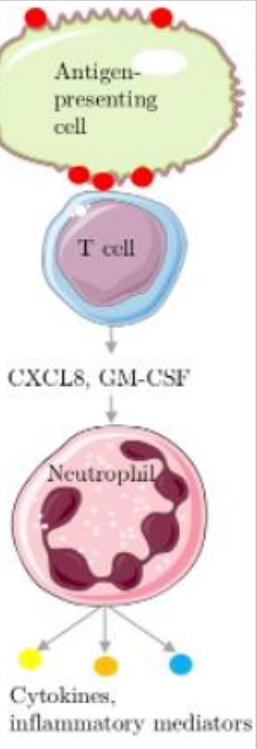
Wurpts 2019 – aktuell in Überarbeitung

Was sind Allergien?

ἄλλος „woanders“ ἔργον „wirken“: Überreaktion auf harmlose Stoffe



Penicillin-Allergie Mechanismen

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Synonym	IgE-mediated	Cytotoxic	Immune complex	Delayed, cell-mediated			
	 <p>Antigen</p> <p>Activation mastcell/basophil</p> <p>Degranulation: Inflammatory mediators (e.g., histamine, heparin, prostaglandins)</p>	 <p>IgG Antibody</p> <p>Target cell</p> <p>Surface antigen</p> <p>Complement protein</p> <p>Complement activation</p> <p>Perforin, Granzymes</p> <p>NK Cell</p> <p>Neutrophil cytotoxicity, opsonization with phagocytosis, cell lysis</p>	 <p>local vascular inflammation</p> <p>Interaction via Fc-IgG receptor with complex</p> <p>Recruitment of neutrophilic granulocytes</p> <p>Immune complexes in blood vessel</p> <p>Complement activation</p> <p>Tissue deposition</p>	 <p>Antigen-presenting cell</p> <p>Often: CD8+ cell recruitment (Type IVc)</p> <p>TH1 cell</p> <p>IFNγ, TNFα</p> <p>Macrophage</p> <p>Chemokines, cytokines cytotoxins</p>	 <p>Antigen-presenting cell</p> <p>TH2 cell</p> <p>IL-4, IL-5, IL-13</p> <p>Eosinophil</p> <p>Cytokines, inflammatory mediators</p>	 <p>Antigen-presenting cell</p> <p>Cytotoxic T cell</p> <p>Granzyme B, perforin</p> <p>kills tissue cells (e.g., keratinocytes, hepatocytes)</p>	 <p>Antigen-presenting cell</p> <p>T cell</p> <p>CXCL8, GM-CSF</p> <p>Neutrophil</p> <p>Cytokines, inflammatory mediators</p>
Clinical Manifestation	Urticaria, angioedema, systemic anaphylaxis	Hemolytic anemia, neutropenia, thrombocytopenia	Serum sickness, arthus reaction (local), vasculitis	CD, MPE	DRESS, MPE	CD, MPE, hepatitis, SJS/TEN, FE, SDRIFE*	AGEP (acute generalized exanthematous pustulosis)
Timing	Minutes-hours	Variable (~2-3 days)	1-3 weeks	2-7 days			

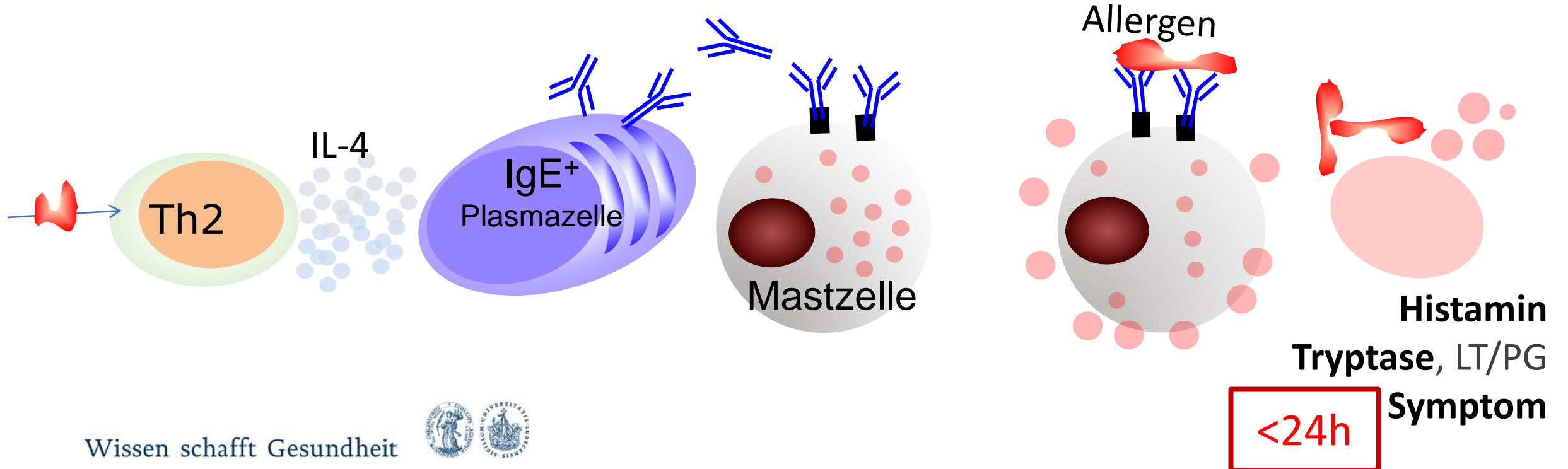
Typ I-Allergien sind chronisch

I. Sensibilisierung
"man wird allergisch"

KEIN Symptom

II. Effektorphase
"Reaktion"

Symptome



Anaphylaxie



= **akute systemische** Reaktion mit Symptomen einer **allergischen Sofortreaktion**, die den ganzen Organismus erfassen kann und **potenziell lebensbedrohlich** ist

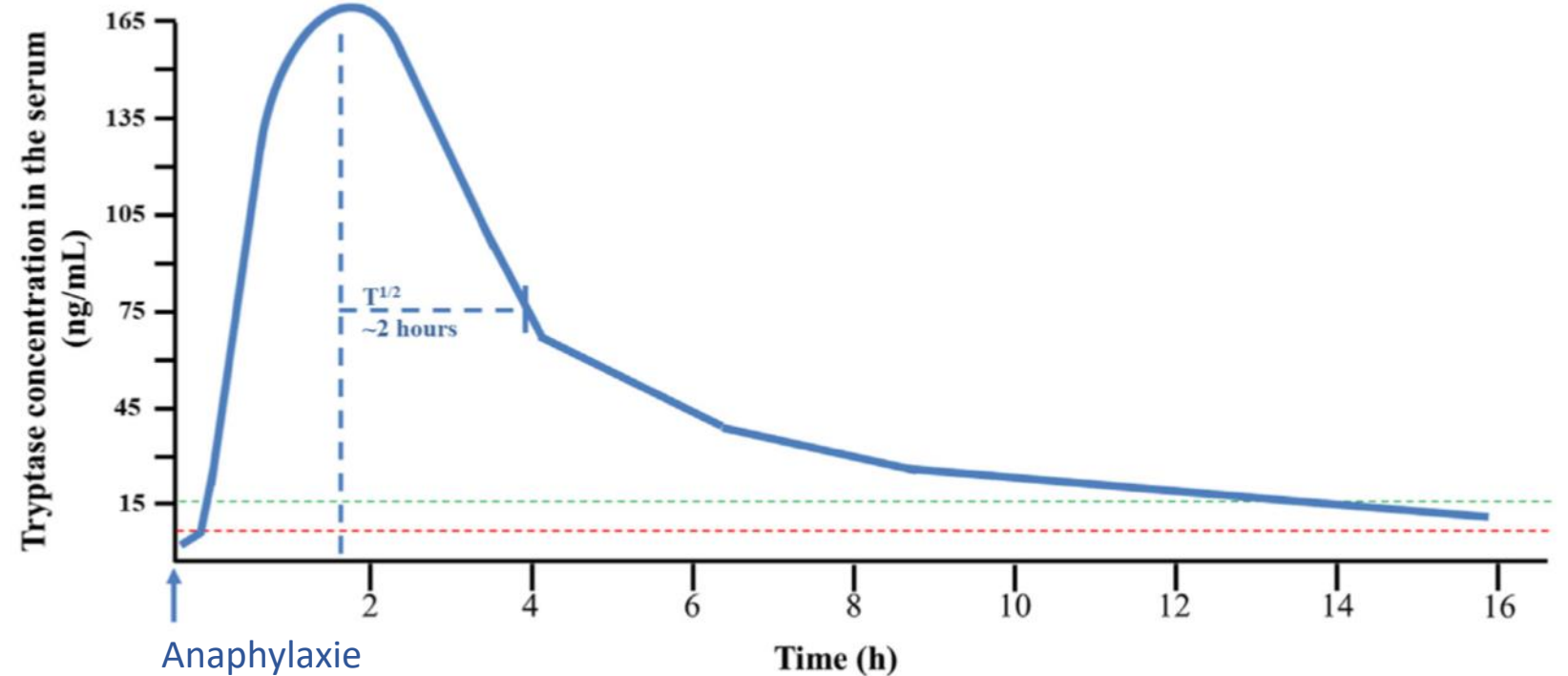
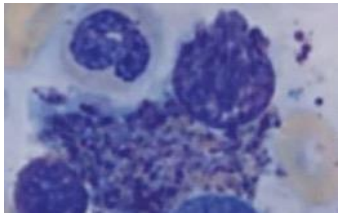
Grad	Haut/Allgemein	Respiration	Abdomen	Kreislauf
I	Juckreiz Urticaria Angioödem	-	-	-
II	Dito	Rhinorrhoe Heiserkeit Dyspnoe	Nausea Krämpfe Erbrechen	Puls +20/Min RR -20 mmHg Arrhythmie
III	Dito	Larynxödem Bronchospasmus Zyanose	Erbrechen Defäkation	Schock
IV	Dito	Atemstillstand	dito	Herz-Kreislauf-Stillstand

Akute Tryptase !

Tryptase

Mastzelle

Toluidinblau



Vergleich akut – basal beweist Anaphylaxie !

Fall 1

5-jähriges Mädchen mit **Zahn-OP**

Einleitung: Ibuprofen, Propofol, Ampi/Sulbactam

15 Min: RR 90/40, Urticaria, Flush, Gesichtsschwellung

-> °__ Anaphylaxie (Adrenalin i.m. + aH1 i.v. + Prednisolon i.v.)

Tryptase akut: 15 µg/L

-nächster Tag: 3.2 µg/L (< 11.4), übernächster Tag: 3.1 µg/L

Allergietestungen

Pricktest



Foto: UKSH



Minispitze >>>

Intracutantest



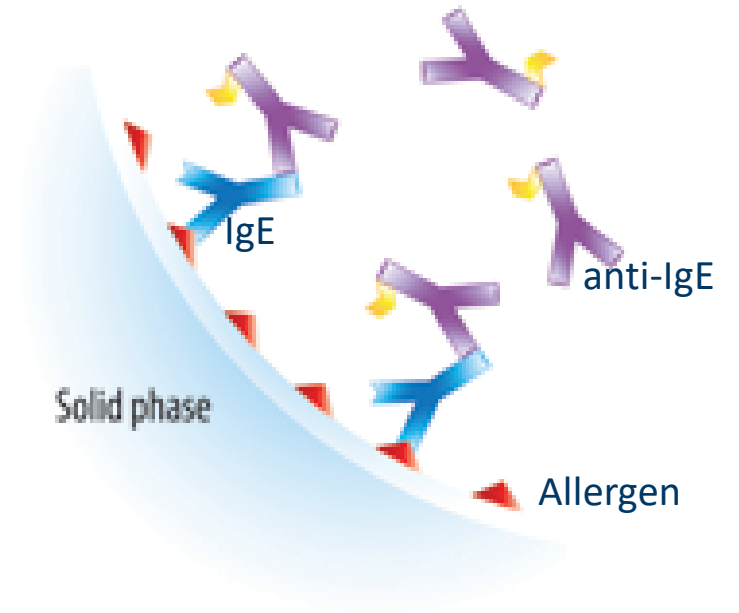
Allergen1

Allergen2

NaCl

Histamin

Serum-IgE



Hohe Spezifität

PenG/V, Ampi/Amoxicilloyl, Cefaclor

Allergietest Beispiel

- Z.n. °III Anaphylaxie (Cfx)
- Kein Bluttest verfügbar
- Keine Expositionstestung mgl.

Testsubstanz	Scratch	Prick	Intra- cutan
1 Clarithromycin	/	+	
2 Accupaque 1:100	/	+	
3 Cefuroxim 1:100	/	+	
4 Accupaque 1:10	/	+	
5 Cefuroxim 1:10	/	+	
6 Accupaque pur	/	+	
7 Cefuroxim pur	/	+	
8 NaCl	/	+	
9 Histamin	/	Stark	



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-nächster Tag: 3.2 µg/L (< 11.4), übernächster Tag: 3.1 µg/L

Testungen opB: Ampicilloyl-/Soja-IgE, Penicilline

Ibuprofen wird vertragen

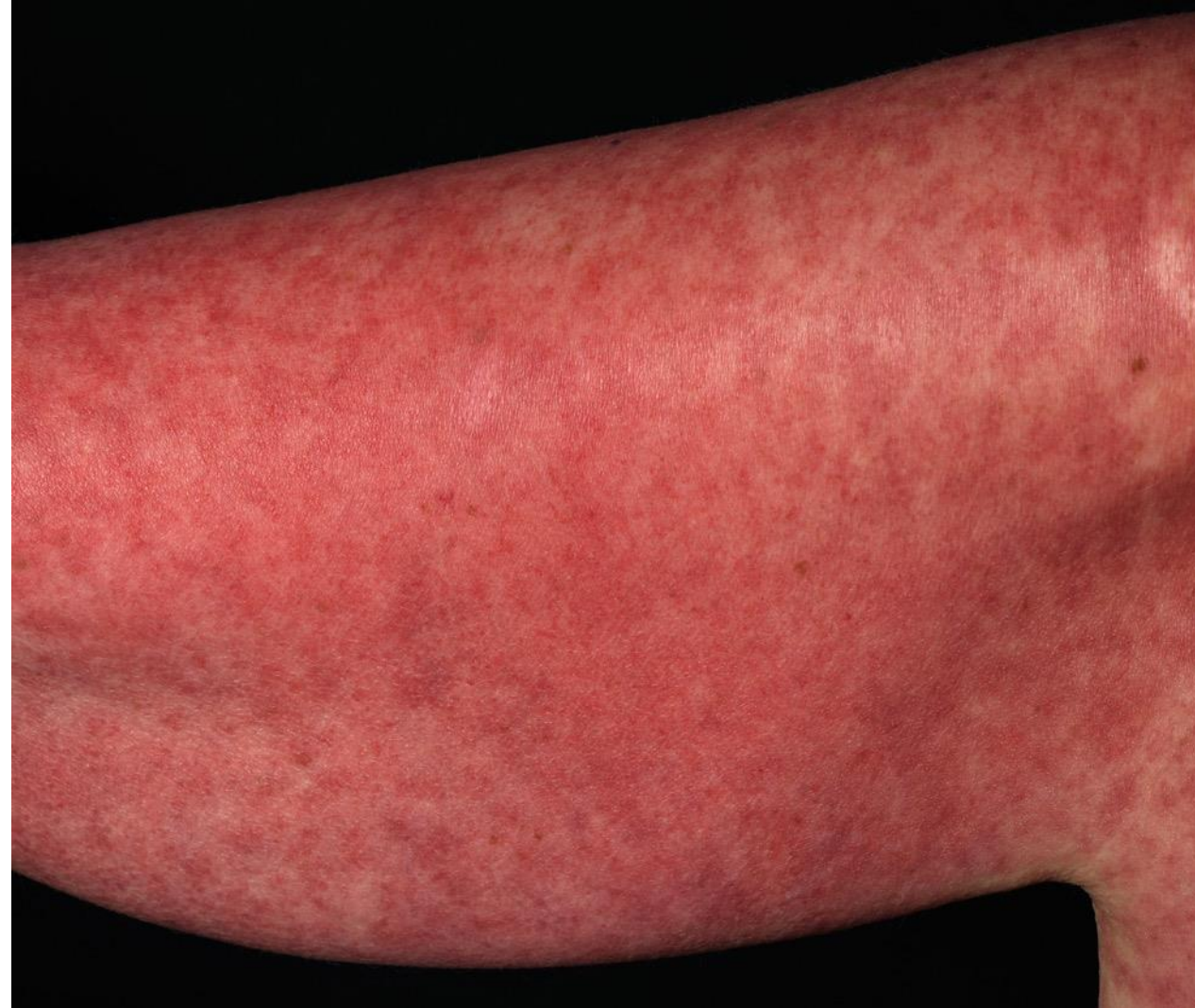
Exposition Phenoxymethylpenicillin (PenV) empfohlen

- **Meistens** makulopapulöse Exantheme
- „benign rash“, juckend, AZ gut
- **Nicht** palmoplantar/mukosa/bullös
- nach mehreren **Tagen Therapie**
- **Spontan** in 1-2 Wochen Besserung
- Prognose sehr gut, **keine Abklärung**



Typ IV-Allergien auf Penicillin

- **Selten** systemische T-Zell-Aktivierung
- Makulopapulöse Exantheme, AZred
auch palmoplantar, mukosa
- **1-3 Tage** nach Beginn; AB-Wechsel,
2-3 Wochen Prednisolon systemisch
- Prognose gut, **allerg. Abklärung**



severe cutaneous adverse reaction



Symmetrical Drug-
Related Intertriginous
and Flexural Exanthema

Generalized Bullous
Fixed Drug Eruption

Akute Gen.
Exanthematische
Pustulose

Tox. epidermale
Nekrolyse



SDRIFE



GBFDE



AGEP



Steven-Johnson
Lyell, EEM

- Noxe ausschalten
- systemisches Glukokortikoid
 - 1 mg/kg Prednisolon, absteigend
- topisches Glukokortikoid
 - epidermaler Beteiligung
- symptomatischer Versuch mit Antihistaminika
 - Typ IVb, nicht kausal
- bei TEN/Lyell:
 - Umkehrisolation, Antibiose
 - Lagerung
 - Ciclosporin, IVIG, TNFi
 - ITS-Maßnahmen

Testung von Typ IV-Allergien

- Unklarer Ausschlag

- Nach Amoxicillin

- Intracutantest

- Spätablesung

- -> Expositionstestung gegen Cefuroxim toleriert

Pricktest – Penicillin

Nr.	Testsubstanz	nach 15 Min.	24h Späte
1	Penicillin V (Phenoxymethylpenicillin)		Ø
2	Penicillin G (Benzylpenicillin)		Ø
3	Ampicillin		10mm
4	Amoxicillin		10mm
5	Cefuroxim		1
6	Clindamycin		8mm
7	BP-OL (rot)		Ø
8	MD (gelb)		Ø
7	NaCl		Ø
8	Histamin	5mm	Ø

1 Tag

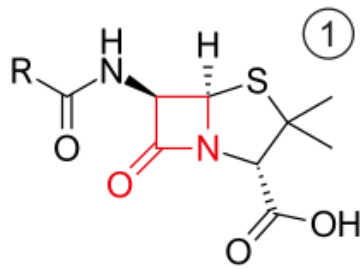
3 Tage



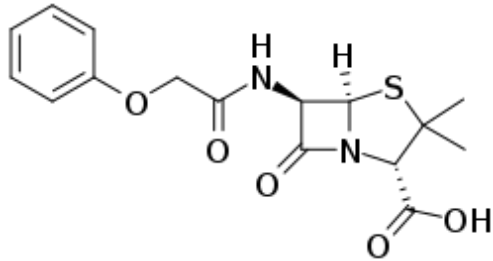
Kreuzreaktivität von Betalaktamantibiotika

- Seitenketten, nicht Betalaktam-Ring ist immunogen

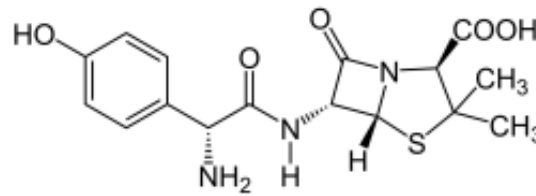
Betalaktam



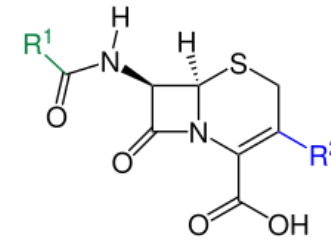
Penicillin V



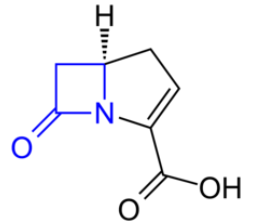
Amoxicillin



Cephalosporin

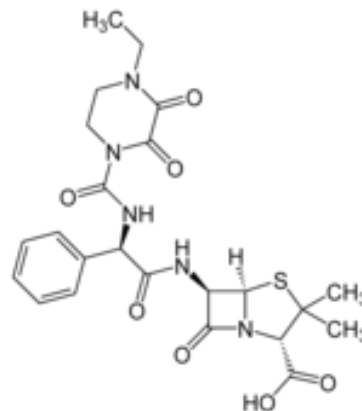


Carbapenem

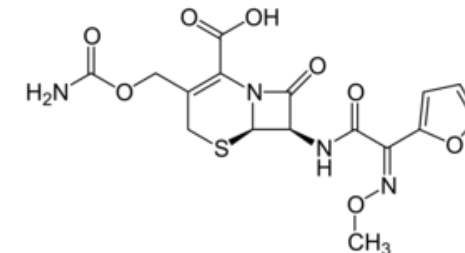


Piperacillin

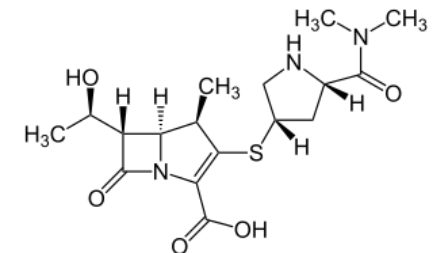
Acylaminopenicillin



Cefuroxim



Meropenem



Kreuzreaktivität von Betalaktamantibiotika

	Cross-tabulation was similar
	Allergy possible based on the formation of PPL
	Potential cross-allergy based on an identical R1 side chain
	Potential cross-allergy based on similarity in R1 or R2 side chains or clinical studies
✓	No risk of a cross-allergic reaction

PPL, polyvalent penicilloyl polylysine (a major penicillin determinant)

<i>β-Lactam Antibiotic</i>	Amoxicillin	Penicillin G	Penicillin V	Flucloxacillin	Feneticillin	Piperacillin	Cephalexin	Cefazolin	Cefalothin	Cefuroxime	Cefaclor	Cefamandol	Ceftibuten	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Cefiderocol	Ceftaroline	Ceftolozane	Meropenem	Imipenem	Ertapenem	Aztreonam
Amoxicillin	Black	Gray	Gray	Gray	Gray	Gray	Yellow	White	White	White	Yellow	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Penicillin G	Gray	Black	Gray	Gray	Gray	Gray	Yellow	White	White	White	Yellow	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Penicillin V	Gray	Gray	Black	Gray	Gray	Gray	Yellow	White	White	White	Yellow	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Flucloxacillin	Gray	Gray	Gray	Black	Gray	Gray	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White
Feneticillin	Gray	Gray	Gray	Gray	Black	Gray	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White
Piperacillin	Gray	Gray	Gray	Gray	Gray	Black	Yellow	White	White	White	Yellow	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Cephalexin	Yellow	Yellow	Yellow	White	White	Yellow	Black	White	White	White	Red	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Cefazolin	White	White	White	White	White	White	White	Black	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White
Cefalothin	White	White	White	White	White	White	White	White	Black	Yellow	White	White	White	White	Yellow	White	White	White	White	White	White	White	White	White
Cefuroxime	White	White	White	White	White	White	White	White	Yellow	Black	White	White	White	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	White	White	White	Yellow
Cefaclor	Yellow	Yellow	Yellow	White	White	Yellow	Red	White	White	White	Black	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Cefamandole	Yellow	Yellow	Yellow	White	White	Yellow	Yellow	White	White	White	Black	Yellow	White	White	White	White	White	White	White	White	White	White	White	White
Ceftibuten	White	White	White	White	White	White	White	White	White	White	White	White	Black	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	White	White	White	Yellow
Ceftriaxone	White	White	White	White	White	White	White	White	White	Yellow	White	White	Yellow	Black	Red	Yellow	Yellow	Yellow	Yellow	Yellow	White	White	White	Yellow
Cefotaxime	White	White	White	White	White	White	White	White	Yellow	White	White	White	Yellow	Red	Black	Yellow	Yellow	Yellow	Yellow	Yellow	White	White	White	Yellow
Ceftazidime	White	White	White	White	White	White	White	White	White	White	White	White	White	Yellow	Yellow	Black	Yellow	Red	Yellow	Yellow	White	White	White	Red
Cefepime	White	White	White	White	White	White	White	White	White	Yellow	White	White	White	Yellow	Yellow	Black	Yellow	Yellow	Yellow	Yellow	White	White	White	Yellow
Cefiderocol	White	White	White	White	White	White	White	White	White	Yellow	White	White	White	Yellow	Yellow	Red	Black	Yellow	Black	Yellow	White	White	White	Red
Ceftaroline	White	White	White	White	White	White	White	White	White	Yellow	White	White	White	Yellow	Yellow	Yellow	Yellow	Black	Yellow	Yellow	White	White	White	Yellow
Ceftolozane	White	White	White	White	White	White	White	White	White	Yellow	White	White	White	Yellow	Yellow	Yellow	Yellow	Yellow	Black	Yellow	White	White	White	Yellow
Meropenem	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	Black	Yellow	Yellow	White	White
Imipenem	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	Black	Yellow	White	White
Ertapenem	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	White	Black	Yellow	White
Aztreonam	White	White	White	White	White	White	White	White	White	Yellow	White	White	Yellow	Yellow	Yellow	Red	Yellow	Red	Yellow	Yellow	White	White	White	Black



Behandlung von Penicillinallergie

Therapie beenden

Typ I-Allergie

- Adrenalin / Intensivmed.
- Antihistaminika
- Glukokortikoid (Infusion/Creme)

Typ IV-Allergie

- Glukokortikoid (Infusion/Creme)

Substanz bis zur Testung meiden

Untersuchung bei Penicillinallergie

Typ I-Allergie

- Pricktest
- Intracutantest
- Sofortablesung
- Bluttest: IgE/Tryptase

Reaktion
Faktoren

Typ IV- Allergie

Intracutantest

- Intracutantest

Spätablesung

**Positivexposition
oder
Ausweichexposition**

Penicillinallergien

- **Typ I-Allergien** -sofort<24h- **Hauttest, Bluttest** (spez.IgE, Intracutantest-15min, Tryptase)
 - **Typ IV-Allergien** –verzögert>24h- **Hauttest** (Epikutantest, Intracutantest-2 Tage)
 - **Provokationstestungen** beweisen oder widerlegen eine Allergie,
und dienen dazu Ausweichstoffe zu identifizieren
- **Penicillinallergien und Kreuzreaktionen sind selten**
- auch bei **Vorliegen einer Penicillinderivatallergie stehen andere** zur Verfügung



Allergiezentrum

Schleswig-Holsteiner
Allergie-Zentrum (SHAZ)

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Vielen Dank für Ihre Aufmerksamkeit